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09/856,812	09/07/2001	Lan-Qing Huang	L0461/7115	3475	
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WOLF GREENFIELD & SACKS, PC			DAVIS, MINH TAM B		
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BOSTON, MA	A 02210-2206		1642		
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Please find below and/or attached an Office communication concerning this application or proceeding.

		Application No.	Applicant(s)				
Office Action Summary		09/856,812	HUANG ET AL.				
		Examiner	Art Unit				
		MINH-TAM DAVIS	1642				
Period for Reply		pears on the cover sheet wit	-				
A SHORTENED STATUTORY WHICHEVER IS LONGER, FF - Extensions of time may be available und after SIX (6) MONTHS from the mailing - If NO period for reply is specified above, - Failure to reply within the set or extended Any reply received by the Office later the earned patent term adjustment. See 37	ROM THE MAILING D er the provisions of 37 CFR 1.1 date of this communication. the maximum statutory period I period for reply will, by statute in three months after the mailin	ATE OF THIS COMMUNIC 36(a). In no event, however, may a re will apply and will expire SIX (6) MONT a, cause the application to become ABA	CATION.  Inply be timely filed  ITHS from the mailing date of this co  ANDONED (35 U.S.C. § 133).				
Status	·	•					
	2b)⊡ This in condition for allowa	September 2006. Se action is non-final. Ince except for formal matter Ex parte Quayle, 1935 C.D.	• •	merits is			
	in the practice under t	_x parte Quayle, 1955 C.D.	11, 455 O.G. 215.				
Disposition of Claims							
<ul> <li>4)  Claim(s) 1,2,4,5,9-11 and 42-54 is/are pending in the application.</li> <li>4a) Of the above claim(s) 10, 51 is/are withdrawn from consideration.</li> <li>5)  Claim(s) is/are allowed.</li> <li>6)  Claim(s) 1,2,4,5,9,11,42-50 and 52-54 is/are rejected.</li> <li>7)  Claim(s) is/are objected to.</li> <li>8)  Claim(s) are subject to restriction and/or election requirement.</li> </ul>							
Application Papers				•			
9)☐ The specification is object	ted to by the Examine	er.					
10)☐ The drawing(s) filed on is/are: a)☐ accepted or b)☐ objected to by the Examiner.							
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).							
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.							
Priority under 35 U.S.C. § 119	objected to by the L.	variiner. Note the attached	Office Action of form F 19	O-132.			
<u> </u>							
<ul> <li>12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).</li> <li>a) All b) Some * c) None of:</li> <li>1. Certified copies of the priority documents have been received.</li> <li>2. Certified copies of the priority documents have been received in Application No</li> <li>3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).</li> <li>* See the attached detailed Office action for a list of the certified copies not received.</li> </ul>							
Attachment(s)							
1) Notice of References Cited (PTO-89 2) Notice of Draftsperson's Patent Drav 3) Information Disclosure Statement(s) Paper No(s)/Mail Date	ring Review (PTO-948)	Paper No(s)	ummary (PTO-413) /Mail Date formal Patent Application				

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 12, 17.

Accordingly, claims 1-2, 4-5, 9, 11, 42-50, 52-54, SEQ ID NO:42, or a nonapeptide comprising an unbroken sequence of SEQ ID NO:1, wherein the amino acid adjacent to the N-terminal amino acid is L and the N-terminal amino acid is L, are being examined.

#### Restriction

1. The response asserts that Applicant requests that the addition species of claims 4, 44, 47 are rejoined with the species the N-terminal amino acid is L and the N-terminal amino acid is L, upon allowance of the pending claims.

After review and reconsideration, the species the N-terminal amino acid is L and the N-terminal amino acid is I in claims 4, 44, 47 is rejoined with the species the N-terminal amino acid is L and the N-terminal amino acid is L, in view of the teaching in the art (see new 102 rejection below).

The consideration of rejoining other species of claims 4, 44 and 47, however, is delayed until the time of allowance, if the claims are allowable.

Accordingly, claims 1-2, 4-5, 9, 11, 42-50, 52-54, SEQ ID NO:42, or a nonapeptide comprising an unbroken sequence of SEQ ID NO:1, wherein the amino acid adjacent to the N-terminal amino acid is L and the N-terminal amino acid is L, or I, are being examined.

2. The response asserts that for the decapeptide of claim 51, although the decapetide may be structurally and functionally distinct from a nonapeptide, claim 51 is dependent on claim 44, and thus requires both structural and functional similarity with the claimed nonapeptide.

The response has been considered, but is not found to be persuasive for the following reasons:

Although the decapeptide of claim 51 requires the binding to HLA-A2, preferably HLA-A2.1, as cited in claim 1 to which claim 44 depends, binding to HLA-A2 is not the critical function of the claimed polypeptide. The critical function of the decapeptide of claim 51 is not predictable, and is not necessarily the same as the nonapeptide of SEQ ID NO:1, in view that the effect of the unknown extra amino acid at either the N-terminal or C-terminal of the nonapeptide of SEQ ID NO:1 on the function of the decapeptide of claim 51 is not predictable.

The requirement is still deemed proper and is therefore made FINAL.

### Claim Rejections - 35 USC § 112, First Paragraph, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 11, 44-50, 52-54 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons already set forth in paper of 04/24/06. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The response recites case law, asserting that there is no written description issue with known polypeptide combined with an unknown sequence to create a new chimeric protein.

The response asserts that the Examiner assertion that there is no correlation between structure and function is incorrect, because the specification describes the peptide binding motifs for HLA-A2 binding peptides, i.e. nonapeptide having Leu or Met at position 2 and Leu, Val or Ile at the C-terminus.

The response has been considered but is not found to be persuasive for the following reasons:

The cited case law is not applicable in the instant application. In a chimeric protein, there is correlation between structure and function, because the attached sequence would not abolish the function of the polypeptide. However, this is not the case for the instant claimed polypeptide, because there is **no correlation between structure and function**, for the following reasons:

- 1) There is no correlation between structure and function for the polypeptide comprising an unbroken sequence of SEQ ID NO:1, which sequence binds with HLA-A2, or HLA-A2.1, because binding to HLA-A2, or HLA-A2.1 is not a critical function of the claimed polypeptide, in view that binding to an HLA molecule per se, even with high affinity, does not necessarily lead to eliciting a T cell response, as taught by Kirkin et al, of record.
- 2) Further, there is no correlation between structure of the claimed sequences and the function of eliciting an immune response or eliciting cytolytic response by T cells specific for SEQ ID NO:1, because the effect of the attached sequences with unknown structure on the conformation of the claimed polypeptide is unpredictable, in view of the teaching of Bowie, of record. Thus, one cannot predict whether the claimed polypeptides would have similar

conformation as SEQ ID NO:1 and expose on its surface said unbroken sequence or nonapeptide of SEQ ID NO:1, such that B cells or T cells specific for said unbroken sequence or nonapeptide of SEQ ID NO:1 would recognize cells expressing the claimed polypeptides,

- 3) In addition, there is no correlation between structure of the claimed sequences and the function of eliciting an immune response or eliciting cytolytic response by T cells specific for SEQ ID NO:1, because the claims encompass a **genus** of peptides, or nonapeptides derived from the MAGE-10 protein SEQ ID NO:1, that are linear or conformational **epitopes of B cells or T cells**, wherein except the two linear peptides SEQ ID NO:42, and SEQ ID NO:44, the structure of which other 9 amino acid peptides of SEQ ID NO:1 are B or T cell epitopes is not disclosed, and is not predictable, in view of the teaching of Kirkin et al, Visseren et al, Stites et al, Herbert et al, and Greenspan et al, all of record, and
- 4) Contrary to the response assertion, there is no disclosure of a common structure that correlates with the ability to elicit T cell response. The recited motifs are only for a nonapeptide that is predicted to bind to HLA-A2. However binding to HLA-A2 per se is not sufficient for predicting a successful elicitation of T cell response, because binding to an HLA molecule per se, even with high affinity, does not necessarily lead to eliciting a T cell response, as taught by Kirkin et al, of record. Further, the recited SEQ ID NO:42 and SEQ ID NO:44 are not representative species, because different fragments of SEQ ID NO:1 are structurally distinct, and would not share the same structure with SEQ ID NO:42 and SEQ ID NO:44, and because not any fragment of a protein would have the property of eliciting a T cell response, in view of the teaching of Kirkin et al, Visseren et al, and Stites et al, all of record.

Thus, the claims and the specification do not meet the standards as shown in the examples of <u>Lilly</u> or <u>Enzo</u>, and one would conclude that Applicant did not have possession of the claimed polypeptides at the time the invention was made.

# Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 1-2, 4-5, 9, 11, 42-50, 52-54 remain rejected under 112, first paragraph, for lack of enablement for 1) A polypeptide "comprising" an unbroken sequence of SEQ ID NO:1, that complexes with HLA-A2, or that elicits an immune response, 2) A nonapeptide comprising an unbroken sequence of SEQ ID NO:1, wherein the amino acid adjacent to the N-terminal amino acid is L and the N-terminal amino acid is L, or a polypeptide of up to about 93 amino acids in length, and comprising said nonapeptide, and 3) A nonapeptide comprising SEQ ID NO:42, for reasons already of record in paper of 04/24/06.

1. The response asserts that the specification contains working examples that MAGE-10 is expressed and processed appropriately to permit recognition by T cells receptors. The response asserts that as shown in Example 5, allogeneic tumor cells that express MAGE-10 are able to stimulate CTLs. The response further asserts that the claimed polypeptide have uses other than the use singled out by the Examiner.

The response has been considered but is not found to be persuasive for the following reasons:

One cannot predict that the polypeptide comprising a fragment of a nonapeptide of SEQ ID NO:1, or the nonapeptide SEQ ID NO:42 could be used for producing antibodies or CTLs effective for diagnosis or treatment of diseases associated with SEQ ID NO:1, and especially

Application/Control Number: 09/856,812

Art Unit: 1642

cancer. Contrary to the response's assertion, Example 5 on pages 33 of the instant specification only discloses CTL recognition of melanoma cell lines that express MAGE-10. One cannot however extrapolate the expression of MAGE-10 protein on cancer cell lines to that of primary cancer tissue, in view of the following reasons: 1) The teaching of the art that due to cell culture artifacts, expression of cancer cells in culture is not predictably in the same as that of primary cancer cells (see Drexler et al, Embleton et al, Hsu et al, Tian et al, Van Dyke et al, Zaslav et al, and Kunkel et al, all of record, and 2) The teaching by De Plaen et al, of record, that as detected by PCR, MAGE-10 mRNA expression in various tumors is very weak, representing less than 1% of that of highly expressed gene. In view of the above teaching in the art, one cannot predict that the MAGE-10 SEQ ID NO:1 is adequately expressed on primary cancer cells, such that it could be recognized by antibodies or CTLs specific for SEQ ID NO:1.

In addition, one cannot predict whether the claimed polypeptides would have similar conformation as SEQ ID NO:1 and expose on its surface said unbroken sequence or nonapeptide of SEQ ID NO:1, such that B cells or T cells specific for said unbroken sequence or nonapeptide of SEQ ID NO:1 would recognize cells expressing the claimed polypeptides for the following reasons: The polypeptide comprising a fragment of a nonapeptide of SEQ ID NO:1 encompasses sequences of unknown structure attached to a 9 amino acid peptide of SEQ ID NO:1. However, the effect of the attached sequences with unknown structure on the conformation of the claimed polypeptide is unpredictable, in view of the teaching of Bowie, of record.

Further, cancer diagnosis and treatment is unpredictable, in view of the teaching in the art concerning the problem with down regulation of the expression of tumor antigens, and cancer tolerance, as taught by White et al, and Smith et al, all of record. Moreover, cancer treatment

using MAGE peptide is unpredictable, in view of the teaching of Kirkin et al, of record, that so far only a single MAGE peptide has been identified as having limited anti-tumor activity in patients. Thus on cannot predict that the polypeptide comprising a fragment of a nonapeptide of SEQ ID NO:1, or the nonapeptide SEQ ID NO:42 could be used for producing antibodies or CTLs effective for diagnosis or treatment of diseases associated with SEQ ID NO:1, and especially cancer.

Further it is not clear what other use is applicable for the claimed polypeptide, or nonapeptide, besides making antibodies or CTLs for diagnosis or treating disease caused by SEQ ID NO:1, or cancer, as contemplated by the instant specification.

2. Concerning the enablement of an unbroken nonapeptide sequence of SEQ ID NO:1, wherein the amino acid adjacent to the N-terminal amino acid is L and the C-terminal amino acid is L, the response asserts that there is only a finite number of the claimed sequence XLXXXXXXL, because the sequence has to be from SEQ ID NO:1. The response asserts that the full sequence MAGE-10 is disclosed, and thus it is only trivial exercise to identify the claimed composition and make them.

The response has been considered but is not found to be persuasive for the following reasons:

Contrary to the response's assertion, screening assays do not enable the claimed invention because the court found in *Rochester v. Searle*, 358 F.3d 916, Fed Cir, 2004, that screening assays, and by inference suggestions of structural analysis, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Application/Control Number: 09/856,812

Art Unit: 1642

Page 9

Although of the claimed sequence XLXXXXXXL is from SEQ ID NO:1, and although the full length SEQ ID NO:1 is disclosed, it would be undue experimentation for one of skill in the art to screen for the claimed sequences, in view that it is unpredictable that the claimed sequence would have the ability to elicit T cell response sufficient for diagnosis or treating diseases, such as cancer. The nonapeptide sequence having the amino acid L as the amino acid adjacent to the N-terminal amino acid L and the C-terminal amino acid is only predictably bind to HLA.A2. However, one cannot predict that the claimed nonapeptide would have sufficient affinity for HLA.A2, and having the ability to elicit T cell response, because of the following reasons:

- 1) Other than SEQ ID NO:42 and SEQ ID NO:44, the amino acids at positions 1, 3, 6 and 7 of the claimed genus of nonapeptides from SEQ ID NO:1 that bind to HLA-A2 and elicit T cell response or an immune response are not disclosed; which amino acids however could have negative effect on the affinity of peptide binding to HLA-A2.1, in view of the teaching of WO 94/0202127 A1.
- 2) Further, Visseren et al teach that even some peptides of MAGE-2, that fit into the binding motif for binding to HLA-A0201, do not bind to the HLA molecule with sufficient affinity (p.127, first column, first paragraph). Indeed, one of the peptide, M2 15-23, which seems to be the same as peptide motif for binding to HLA-A2 as the claimed nonapeptide of claim 4, does not bind to HLA-A2 with sufficient affinity (Visseren et al, table I on page 127). Further, Visseren et al teach even some peptides that bind to the HLA molecule with high affinity at 4° C, they do not bind with high affinity at 37° C, and therefore are less likely to form stable complexes in vivo and have a lower chance to appear in HLA-A0201 molecule at the cell surface

(p.127, first column, second paragraph). Visseren et al teach that not all peptides from MAGE-2 are immunogenic and produce an immune response in vivo in mice (p.127, first column, third paragraph).

3) In addition, although several peptides of melanoma associated antigens have been identified as recognized by CTL in vitro, and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response in vivo, so far only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (Kirkin et al, of record).

Thus in view of the above teaching of in the art, one cannot predict that the claimed nonapeptides would bind to HLA-A2 molecule with sufficient affinity to induce an immune response or a CTL response useful for diagnosis or treatment of diseases associated with SEQ ID NO:1, such as cancer. Because of such unpredictability, it would be undue experimentation for one of skill in the art to screen for the claimed polypeptide.

#### Claim Rejections - 35 USC § 102

Claims 4, 11, 42-43 remain rejected under 102(e) as being anticipated by US 6,682,731.

The response asserts that the claims have been amended to exclude the peptide SEQ ID NO:20 of US 6,682,731, which is the same as the claimed SEQ ID NO:50.

The response has been considered but is not found to be persuasive for the following reasons:

Rejection remains, because the limitation of excluding SEQ ID NO:50 is not found in claims 4, 11, 42-43.

# New Rejection Based on the Amendment and New Consideration

#### **Objection**

Claims 1-2, 44-50, 52-54 are objected to, because claims 1, 2 are confusing. Claims 1-2, reasonably reads on a polypeptide of any size, provided that it comprises a sequence of SEQ ID NO:1, that binds to HLA-A2, or elicits an immune response, including a polypeptide consisting of a nonapeptide of SEQ ID NO:1, that binds to HLA-A2, such as SEQ ID NO:42. It is not clear how the claimed polypeptide, such as the nonapeptide SEQ ID NO:42, is not that set out *in* SEQ ID NO:1.

# Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4, 11, 42, 44-45, 47-48, 50, 52-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Registry Number 53665-55-7, as taught in Okada et al, 1974 (Tetrahedron, 30(10): 1175-85).

Claim 1. (Currently amended) An isolated polypeptide comprising an unbroken sequence of amino acids from SEQ ID NO: 1 that complexes with a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1, wherein the amino acid sequence of said isolated polypeptide is not that set out in either of SEQ ID NOs: 1 and 2, or that coded for by nucleotides 334-918 of SEQ ID NO:7, or GLEGAQAPL (SEQ ID NO:50).

Claim 2. (Currently amended) An isolated polypeptide comprising an unbroken sequence of amino acids from SEQ ID NO: 1, that elicits an immune response from human lymphocytes, wherein the amino acid sequence of said isolated polypeptide or protein is not that set out in either of SEQ ID NOs: 1 and 2, or that coded for by nucleotides 334-918 of SEQ ID NO:7, or GLEGAQAPL (SEQ ID NO:50).

Claim 4. (Currently amended) A nonapeptide comprising an unbroken sequence of amino acids from SEQ ID NO: 1, wherein the amino acid adjacent to the N-terminal amino acid is L or M, and the C-terminal amino acid is L, V, or I, other than a nonapeptide having the sequence CLGLSYDGL (SEQ ID NO:57).

Claim 11. (Previously presented) An isolated polypeptide of up to about 93 amino acids in length, characterised by comprising a nonapeptide as claimed in claim 4.

Claim 42. (Previously presented) The nonapeptide of claim 4, wherein the amino acid adjacent to the N-terminal amino acid is L.

Claim 44. (Previously presented) The isolated polypeptide of claim 1, the polypeptide being a nonapeptide wherein the amino acid adjacent to the N-terminal amino acid is L or M, and the C-terminal amino acid is L, V, or I.

Claim 45. (Previously presented) The isolated polypeptide of claim 44, wherein the amino acid adjacent to the N-terminal amino acid is L.

Claim 47. (Previously presented) The isolated polypeptide of claim 2, the polypeptide being a nonapeptide wherein the amino acid adjacent to the N-terminal amino acid is L or M, and the C-terminal amino acid is L, V, or I.

Application/Control Number: 09/856,812

Art Unit: 1642

Claim 48. (Previously presented) The isolated polypeptide of claim 47, wherein the amino acid adjacent to the N-terminal amino acid is L.

Claim 50. (Currently amended) A polypeptide as claimed in claim 1, other than a nonapeptide having any one of amino acid sequences:

- (a) FLLFKYQMK (SEQ ID NO:48); or
- (b) FIEGYCTPE (SEQ ID NO:49)

Claim 52. (Previously presented) The isolated polypeptide of claim 1, wherein the polypeptide elicits an immune response from human lymphocytes.

Claim 53. (Previously presented) The isolated polypeptide of claim 52, wherein the polypeptide elicits an immune response from human lymphocytes when complexed with a major histocompatibility complex molecule type HLA-A2.

Claim 54. (Previously presented) The isolated polypeptide of claim 52, wherein the immune response is a cytolytic response from human T-lymphocytes.

It is noted that a polypeptide of up to about 93 amino acids in length as claimed in claim 11 could be of any length, provided it is not more than 93 amino acids in length.

Okada et al teach a peptide, VLAVLSLSI, having Registry Number 53665-55-7, which is a peptide of SEQ ID NO:1, wherein the amino acid adjacent to the N-terminal amino acid is L and the C-terminal amino acid is I (Search report, 2006, pages 1-2).

Although the reference does not explicitly teach that the peptide is from SEQ ID NO:1, is not coded by nucleotides 334-918 of SEQ ID NO:7, or SEQ ID NO:50, wherein the peptide binds to HLA-A2, or preferably HLA-A2.1, or elicits an immune response from human lymphocytes, which is a cytolytic response, however, the claimed polypeptide or nonapeptide

appears to be the same as the prior art peptide. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Application/Control Number: 09/856,812 Page 15

Art Unit: 1642

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <a href="http://pair-direct.uspto.gov">http://pair-direct.uspto.gov</a>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS November 20, 2006

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER